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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/405,032	09/24/99	BOYLE W	A-378-CIP2C2

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EXAMINER	
DEBERRY, R	
ART UNIT	**PAPER NUMBER**
1647	6

DATE MAILED: 03/28/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/405,032	Applicant(s) BOYLE ET AL.	
	Examiner Regina M. DeBerry	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *61-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *61-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3 and 6* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

Status of Application, Amendments and/or Claims

The information disclosure statement filed 24 November 1999 (Paper No. 3) was received and complies with the provisions of 37 CFR §§1.97 and 1.98. It has been placed in the application file and the information referred to therein has been considered as to the merits. The amendment filed 24 September 1999 (Paper No. 2) has been entered in full. Claims 1-60 are cancelled. New claims, 61-68 are under examination.

Sequence Rules

The instant application fails to fully comply with the sequence rules 37 CFR 1.821-1.825 because each disclosure of a sequence embraced by the definitions set forth in the rules fails to refer to the required sequence identifier (SEQ ID NO:). This occurs in figures 1A-B, 2B-E, 9A-F, 10, 12A-B, and 14A.

Objection to Specification

The disclosure is objected to because of the following informalities: The description fails to refer to parts of figures 16A-B and 23D.

Drawings

The formal drawings were approved by the draftsman.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 61-68 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 61-68 are drawn to a method for treating bone loss in a mammal comprising administering to the mammal an expression vector comprising a nucleic acid sequence encoding osteoprotegerin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 61-68 are directed to somatic cell gene therapy. In Example 3, the nucleic acid of osteoprotegerin was injected into embryos and transferred to mice. The offspring (transgenic mice) were then sacrificed for necropsy and pathological analysis. While some of the transgenic mice exhibited the effects of overexpressing osteoprotegerin (increased density of the skeleton, decreased trabecular osteoclasts, etc), a normal mice is not an acceptable model for bone loss. To demonstrate inhibition of bone resorption, one would have to show that an initial defect existed and the addition of osteoprotegerin prevented this effect. Furthermore, a transgenic mouse is not predictive of what would happen when one provides gene therapy to a diseased human.

Somatic cell gene therapy is unpredictable in the art (for review see Verma *et al.*, Eck *et al.* and Anderson). There are many technical problems such as delivery, random integration of vector DNA into the host chromosome and efficient/sustained expression of the protein. The choice of vectors and promoters are very important in gene therapy. The specification states that the osteoprotegerin gene was cloned into a liver specific expression vector (pg 44, lines 4-26). What is the significance of using this particular vector versus a kidney specific expression vector? In addition, claims 61-68 are not enabled because it does not state that osteoprotegerin protein has been expressed.

The specification is also not enabled for a method of treating bone loss in a mammal comprising administering to the mammal an expression vector comprising a nucleic acid encoding the polypeptide in SEQ ID NO: 124 wherein the polypeptide comprises from 1 to 216 amino acid residues deleted from the carboxy terminus, wherein the nucleic acid encodes a polypeptide in SEQ ID NO: 124 comprising residues 22-185, 22-189, 22-194, or 22-201, and substitutional variants of SEQ ID NO: 124. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in

binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo *et al.*, 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation.

The specification has "suggested" that amino acid residues 22-185 define a region for OPG activity (page 124, line 20-25) and has tested some variant/deletion OPG constructs *in vitro* (page 123, Table 1). This may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick *et al.*, 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks *et al.*, 1998, Trends in Genetics 14:248-250; Smith *et al.*, 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork *et al.*, 1996, Trends in Genetics 12:425-427). In addition, this does not demonstrate a treatment for bone loss in a mammal.

Due to the large quantity of experimentation necessary to demonstrate a method for treating bone loss in a mammal comprising administering to the mammal an expression vector comprising a nucleic acid encoding the polypeptide of SEQ ID NO: 124 and SEQ ID NO:124 wherein the polypeptide comprises from 1 to 216 amino acid residues deleted from the carboxy terminus, wherein the nucleic acid encodes a polypeptide in SEQ ID NO: 124 comprising residues 22-185, 22-189, 22-194, or 22-201 and substitutional variants, the complex nature of the invention, the unpredictability of the effects of mutation on protein structure/function and the complications of gene therapy regarding delivery, cell targeting, and efficient expression, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

Claims 61-68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 61 is drawn to a method for treating bone loss in a mammal comprising administering to the mammal an expression vector comprising a nucleic acid sequence encoding osteoprotegerin. The term osteoprotegerin is not limited to any specific protein. The metes and bounds of osteoprotegerin cannot be determined from the claim.

Claim 61 does not convey to the skilled artisan the structural and functional requirements of osteoprotegerin to satisfy the limitations of the claims.

Claims 61-68 are indefinite because they are incomplete. Claims 61-68 do not have a cause and effect. The method as pointed out in the preamble must demonstrate an end result.

Claim 62b and 62c are indefinite. Claim 62 is drawn to the method of Claim 61 wherein the nucleic acid sequence is selected from the group consisting of: a) a nucleic acid encoding a polypeptide comprising the amino acid sequence from residues 1 to 401 or from residues 22 to 401 as shown in Figure 9C-D (SEQ ID NO:124):

b) a nucleic acid encoding the polypeptide as in (a) wherein the polypeptide comprises from 1 to 216 amino acid residues deleted from the carboxy terminus: and

c) a nucleic acid which hybridizes under high stringency conditions with the nucleic acid set forth in (a) and (b) wherein the hybridizing nucleic acid encodes a polypeptide having the activity of inhibiting bone resorption.

Claim 62b is indefinite because it is unclear how the polypeptide can both comprise a defined sequence and comprise a deletion of part of that. It is unclear exactly what structures the claim now encompasses. A possible suggestion would be to recite the claim as follows "a nucleic acid encoding the polypeptide as in (a) wherein the polypeptide differs from a polypeptide comprising the amino acid sequence from residues 1-401 or from residues 22-401 by deletions comprising from 1 to 216 amino acid residues deleted from the carboxy terminus". Claim 62c is indefinite because stringency is relative, and the art does not recognize a single set of conditions as

stringent. The specification also does not provide an unambiguous definition for the term. In the absence of a recitation of clear hybridization conditions (e.g., "hybridizes at wash conditions of A X SSC and B % SDS at CoC"), the claims fail to define the metes and bounds of the varying structures of polynucleotides recited in the claimed methods.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (703) 305-6915. The examiner can normally be reached on Mondays-Fridays 8:00 a.m. - 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-7939 for regular communications and (703) 308-2742 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

RMD
March 22, 2001

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER